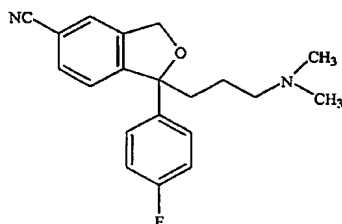


## We claim

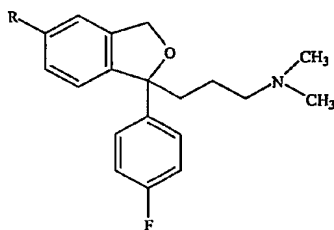
- 1) A process for the preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base, a compound of formula 1,



Formula 1

comprising,

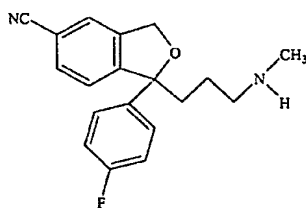
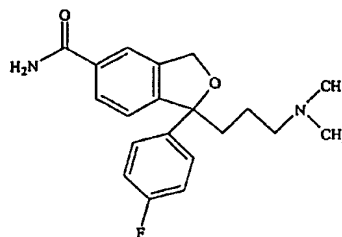
- a) reacting a compound of formula 2, wherein R is Cl or Br,



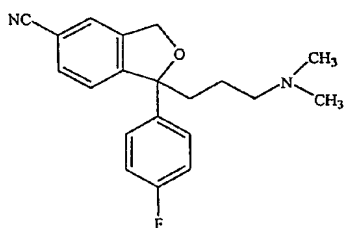
Formula 2

with a cyanide source in presence of an iodide and a suitable solvent selected from the group consisting of amides, amines and polyethers, to obtain the compound of formula 1,

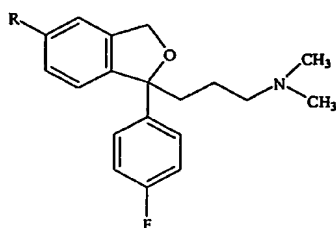
- b) treating the resultant crude compound of formula 1 obtained in step a) containing the desmethylcitalopram impurity viz., 1-[3-(methylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, a compound of formula 3, and the amide impurity viz. 5-carboxamide -1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-phthalide, a compound of formula 4,

**Formula 3****Formula 4**

- with a cyanide reversal agent, wherein the cyanide reversal agent is selected from phosphorous oxyhalides and phosphorous oxides; and isolating the base of compound of formula 1 from the reaction mixture, wherein the compound of formula 1 obtained after isolation has substantially low levels of impurities of formula 3 and formula 4, and optionally converting the compound of formula 1 obtained after isolation, to a pharmaceutically acceptable salt thereof, followed by the conversion of the salt of compound of formula 1 to the base of compound of formula 1,
- c) further purifying the resultant compound of formula 1 obtained in step 'b', from a solvent system, wherein the solvent system comprises a first solvent which is a hydrocarbon solvent and a second solvent, wherein the second solvent is selected from a group consisting of alcohol, ester, ether, ketone or mixture thereof.
- 2) A process for the preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base, a compound of formula 1,

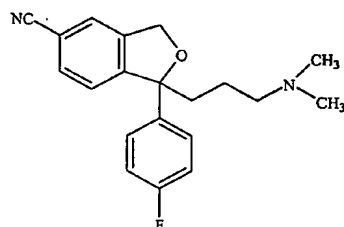
**Formula 1**

comprising reacting a compound of formula 2, wherein R is Cl or Br,

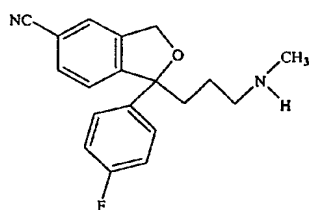
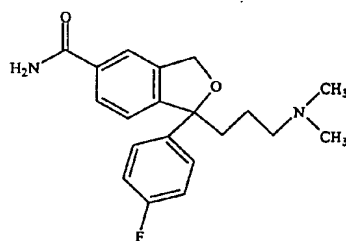
**Formula 2**

with a cyanide source in presence of an iodide and a suitable solvent selected from the group consisting of amides, amines and polyethers.

- 5 3) A process for preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base, a compound of formula 1,

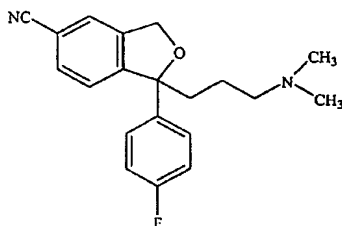
**Formula 1**

- 10 with substantially low levels of impurities, comprising treating the crude compound of formula 1, containing the desmethylocitalopram impurity viz., 1-[3-(methylamino)propyl]-1-(4-fluorophenyl)-1,3- (dihydro-5-isobenzofuran carbonitrile, a compound of formula 3, and the amide impurity viz. 5-carboxamide -1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-phthalide, a compound of formula 4,

**Formula 3****Formula 4**

with a cyanide reversal agent, wherein the cyanide reversal agent is selected from phosphorous oxyhalides and phosphorous oxides; and isolating the base of compound of formula 1 from the reaction mixture, and optionally converting the compound of formula 1 obtained after isolation, to a pharmaceutically acceptable salt thereof, followed by the conversion of the salt of compound of formula 1 to the base of compound of formula 1.

- 4) A process for purification of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, a compound of formula (1), comprising



Formula 1

crystallizing the compound of formula 1 from a solvent system, wherein the solvent system comprises a first solvent which is a hydrocarbon solvent and a second solvent, wherein the second solvent is selected from a group consisting of alcohol, ester, ether, ketone or mixture thereof.

- 5) The process as claimed in claim 2 wherein the cyanide source is selected from the group consisting of KCN, NaCN, CuCN and  $[R_1R_2R_3R_4N]CN$ , wherein  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_4$  are the same or different groups selected from hydrogen and straight chain or branched alkyl.
- 6) A process as claimed in claim 2 wherein the iodide is selected from the group of stable metal iodides, alkali and alkaline earth metal iodides.
- 7) The process as claimed in claim 2 wherein the cyanide source is CuCN, the iodide is potassium iodide and the group R in compound of formula 2 is Br.
- 8) The process as claimed in claim 2 wherein the reaction of compound of formula 2 with a cyanide source is carried out in an amine solvent wherein the amine solvent is selected from pyridine and lutidine.

- 9) The process as claimed in claim 2 wherein the reaction of compound of formula 2 with a cyanide source is carried out at a temperature between the range of about 100°C to about 200°C for about 10 to about 30 hours.
- 10) The process as claimed in claim 9 wherein the reaction of compound of formula 2 with a cyanide source is carried out at a temperature between the range of about 130°C to about 150°C for about 20 to about 28 hours.
- 11) The process as claimed in claim 3 wherein the cyanide reversal agent is phosphorous oxychloride.
- 12) The process as claimed in claim 3 wherein the cyanide reversal agent is phosphorous pentoxide.
- 13) The process as claimed in claim 3, wherein after treatment of compound of formula 1 with a cyanide reversal agent, the resultant compound of formula 1 contains less than about 1% desmethylcitalopram, a compound of formula 3 and less than about 1% amide, a compound of formula 4, after isolation from the reaction mixture.
- 14) The process as claimed in claim 3, wherein after treatment of compound of formula 1 with a cyanide reversal agent, the resultant compound of formula 1 contains less than about 0.5% desmethylcitalopram, a compound of formula 3 and less than about 0.5% of the amide, a compound of formula 4, after isolation from the reaction mixture, characterized in that the cyanide reversal agent is phosphorous oxychloride.
- 15) The process as claimed in claim 3 wherein the ratio of the cyanide reversal agent to the crude compound of formula 1 containing the impurities of formula 3 and formula 4, is in the range from about 0.1 to about 5.
- 16) The process as claimed in claim 3 wherein the ratio of the cyanide reversal agent to the crude compound of formula 1 containing the impurities of formula 3 and formula 4, is in the range from about 0.1 to about 2.
- 17) The process as claimed in claim 3 wherein the ratio of the cyanide reversal agent to the crude compound of formula 1 containing the impurities of formula 3 and formula 4, is in the range from about 0.2 to about 2.

- 18) The process as claimed in claim 3 wherein the reaction of the crude compound of formula 1 containing the impurities of formula 3 and formula 4, with a cyanide reversal agent is carried out in an aprotic organic solvent.
- 19) The process as claimed in claim 18 wherein the aprotic organic solvent is selected from the group consisting of ethers, halogenated solvents, aliphatic hydrocarbons, aromatic hydrocarbons, esters, nitriles and nitro compounds.
- 20) The process as claimed in claim 19 wherein the aromatic hydrocarbon solvent is selected from toluene and xylenes.
- 21) The process as claimed in claim 3 wherein the reaction of the crude compound of formula 1 containing the impurities of formula 3 and formula 4, with a cyanide reversal agent is carried out at a temperature between the range of ambient to about 200°C for about 1 to about 20 hours.
- 22) The process as claimed in claim 21 wherein the reaction is carried out at a temperature between the range of about 50°C to about 150°C for about 1 to about 5 hours.
- 23) The process as claimed in claim 4 wherein the hydrocarbon solvent is a cyclic aliphatic hydrocarbon solvent.
- 24) The process as claimed in claim 23 wherein the cyclic aliphatic hydrocarbon solvent contains 5 to 12 carbon atoms.
- 25) The process as claimed in claim 24 wherein the cyclic aliphatic hydrocarbon solvent is cyclohexane.
- 26) The process as claimed in claim 4 wherein the second solvent is selected from the group consisting of ester, ether, ketone or mixture thereof.
- 27) The process as claimed in claim 4 wherein the second solvent is an alcohol.
- 28) The process as claimed in claim 27 wherein the alcohol is a primary alcohol containing 1 to 5 carbon atoms.
- 29) The process as claimed in claim 27 wherein the alcohol is selected from n-propanol and isopropanol.
- 30) The process as claimed in claim 4 wherein the % solvent ratio of the first solvent to the second solvent is between the range of 99:1 to 60:40.

- 31) The process as claimed in claim 30 wherein the % solvent ratio of the first solvent to the second solvent is between the range of 99:1 to 75:25.
- 32) The process as claimed in claim 31 wherein the % solvent ratio of the first solvent to the second solvent is between the range of 98:2 to 80:20.
- 5 33) The process as claimed in claim 27 wherein the hydrocarbon is cyclohexane and alcohol is n-propanol.
- 34) The process as claimed in claim 27 wherein the hydrocarbon is cyclohexane and alcohol is isopropanol.
- 35) The process as claimed in claim 26 wherein the hydrocarbon is cyclohexane and  
10 ethyl acetate is selected as the ester second solvent.
- 36) The process as claimed in claim 26 wherein the hydrocarbon is cyclohexane and diethylether is selected as the ether second solvent.
- 37) The process as claimed in claim 26 wherein the hydrocarbon is cyclohexane and acetone is selected as the ketone second solvent.
- 15 38) The process as claimed in claim 4 wherein the solvent system used for purification of compound of formula 1 is heated at a temperature between the range of about 40°C to about 150°C.
- 39) The process as claimed in claim 38 wherein the solvent system used for purification of compound of formula 1 is heated at a temperature between the  
20 range of about 50°C to about 80°C.
- 40) The process as claimed in claim 39 wherein the solvent system used for purification of compound of formula 1 is heated at a temperature between the range of about 60°C to about 80°C.
- 41) The process as claimed in claim 1 wherein,  
25 a) a compound of formula 2 wherein R is Br, is reacted with CuCN in presence of potassium iodide, in pyridine solvent to obtain the compound of formula 1,  
b) the resultant crude compound of formula 1 obtained in step a) is treated with POCl<sub>3</sub> and the compound of formula 1 is isolated from the reaction mixture, and optionally converted to a pharmaceutically acceptable salt thereof,  
30 followed by the conversion of the salt of compound of formula 1 to the base of compound of formula 1,

- c) the resultant compound of formula 1 obtained in step b) is purified from a solvent system comprising cyclohexane as the first solvent and n-propanol or isopropanol as the second solvent.
- 42) The process as claimed in any of claims 1, 4 or 41 wherein the compound of formula 1 obtained is further converted to its hydrobromide salt.
- 5 43) The process as claimed in any of claims 1, 4 or 41 wherein the compound of formula 1 obtained is further converted to citalopram hydrobromide having a HPLC purity greater than 99.5%.